CANCER ASSESSMENT DOCUMENT

EVALUATION OF THE CARCINOGENIC POTENTIAL OF
Glyphosate

FINAL REPORT
September 28, 2015

CANCER **A**SSESSMENT **R**EVIEW **C**OMMITTEE
HEALTH EFFECTS DIVISION
OFFICE OF PESTICIDE PROGRAMS
U.S Environmental Protection Agency

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EXECUTIVE SUMMARY

I. INTRODUCTION

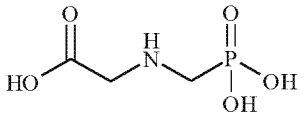
On September 16, 2015 the Cancer Assessment Review Committee (CARC) of the Health Effects Division of the Office of Pesticide Programs met to re-evaluate the carcinogenic potential of glyphosate.

II. BACKGROUND INFORMATION

Glyphosate (*N*-(phosphonomethyl) glycine) is a nonselective herbicide that is currently registered for pre- and post-emergence application to a variety of fruit, vegetable, and field crops. Tolerances are currently established for residues of glyphosate in/on various plant commodities at 0.2-400 ppm (40 CFR §180.364(a) (1). Registered uses range from tree nuts, citrus, and grapes to corn, soybeans, cotton, and rice. Glyphosate is also registered for use on transgenic crop varieties such as canola, corn, cotton, soybeans, sugar beets, and wheat. Aquatic and terrestrial registered uses of glyphosate include non-selective control of nuisance aquatic weeds, ornamentals, greenhouses, residential areas, ornamental lawns and turf, fallow land, pastures, and nonagricultural rights-of-way.

The chemical structure and nomenclature for glyphosate is presented in Table 1.

Table 1. Chemical Nomenclature of Glyphosate

Compound	
Common name	Glyphosate
Company experimental name	DPX-B2856
IUPAC/CAS name	*N*-(phosphonomethyl)glycine
CAS registry number	1071-83-6

Glyphosate is formulated in liquid and solid forms, and it is applied using ground and aerial equipment. Application rates of glyphosate to food crops range from <1 pound (lb) of acid equivalent (ae) per acre (A) for a variety of crops to approximately 15 lb ae/A for spray and spot treatments of crops including tree nuts, apples, citrus, and peaches. Residential lawn and turf application rates range from <1 lb ae/A to approximately 10.5 lb ae/A.
The application timing of glyphosate is varied. Glyphosate can be applied early and late in the season, at pre-plant, planting, pre-emergence, pre-bloom, bud stage, pre-transplant, pre-harvest, post-plant, post-transplant, post-bloom, and post-harvest. It can also be applied during dormant stages and to fallow land, established plantings, stubble, and when needed. In September 1993, the agency issued the glyphosate Reregistration Eligibility Decision (RED) document (D362745). Available from [HYPERLINK "http://www.epa.gov/opp00001/chemsearch/reg%20action/reregistration/red%20PC-417300%201-Sep-93"], pdf

In 1985, the agency, in accordance with the Proposed Guideline for Carcinogen Risk Assessment, classified glyphosate as a Group C chemical; Possible Human Carcinogen based on the presence of kidney tumors in male mice. There was no evidence for carcinogenicity in male or female rats. Furthermore, there were no mutagenicity concerns (TXR No.0052067).

In 1986, the agency requested the FIFRA Scientific Advisory Panel (SAP) to evaluate the carcinogenic potential of glyphosate. On February 24, 1986, the SAP recommended that glyphosate should be categorized as a Group D chemical; Not Classifiable as to Human Carcinogenicity. The panel determined that the data on renal tumors in male mice were equivocal: they were only adenomas, and the increase did not reach statistical significance. The panel also advised the agency to issue a data call-in notice for further studies in rats and/or mice to clarify unresolved questions (SAP Report, 02/24/1986). Available at [HYPERLINK "http://www.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-103601_24-Feb-86_209.pdf"]

In 1991, the Carcinogenicity Peer Review Committee (CPRC) of the Health Effects Division, Office of Pesticide Programs, in accordance with the agency's 1986 *Draft Guidelines for Carcinogen Risk Assessment,* classified glyphosate as a "Group E" chemical: evidence of non-carcinogenicity for humans. This classification was based upon lack of evidence for carcinogenicity in mice and rats and the lack of concern for mutagenicity (TXR# 0008898).

In 2002, the European Union (EU) concluded that there was no evidence of carcinogenicity for glyphosate in long-term studies with mice and rats (EU, 2002).

In 2004, the Joint FA0/WHO Meeting on Pesticide Residues (JMPR) concluded that there was no evidence of carcinogenicity for glyphosate in long term studies in mice and rats and there was no evidence for genotoxic potential (JMPR, 2004).

In 2015, the International Agency for Research on Cancer (IARC) classified glyphosate as a Group 2A chemical; Probable Human Carcinogen based on limited evidence of carcinogenicity in humans and sufficient evidence in experimental animals. The limited evidence in humans was based on a positive association between non-Hodgkin's lymphoma and glyphosate exposure from published epidemiology studies. The sufficient evidence in experimental animals was based on positive trend in the incidence of renal tubular carcinoma and of renal tubule adenoma/carcinoma combined in male CD-1 mice in one study and on the positive trend in the incidence of hemangiosarcomas in male CD-1 mice in another study (IARC, 2015).

In 2015, two chronic toxicity/carcinogenicity studies in rats (MRID Nos. 49631701 and 4970460) and one carcinogenicity study in mice (MRID No. 49631702) that were reviewed by IARC but were not previously available to the agency, were submitted and reviewed. This weight of evidence assessment by the CARC includes all the studies (epidemiology and experimental

animals) reviewed by IARC as well as a subset of animal studies reported in a review article by Greim *et al.,* 2015 reviewed by IARC.

III. EPIDEMIOLOGY

This section includes a review of epidemiologic cohort and case-control studies of glyphosate to evaluate whether exposure to glyphosate is associated causally with the risk of developing cancer in humans.

The Agricultural Health Study (AHS) is a large prospective study conducted in Iowa and North Carolina. Participants (private and commercial applicators) were asked to complete a 21-page questionnaire that included data on personally mixing and/or applying pesticides (including glyphosate), and frequency (days of use per year) and duration (years of use) of pesticide use. Data on the use of personal protective equipment, other farming practices, dietary and lifestyle information, demographic data, and medical information were also collected via the questionnaire (Alavanja *et al.,* 1996). The role of pesticide use and lymph hematopoietic cancers and particularly non-Hodgkin lymphoma (NHL) has been studied in several investigations. For most of the cancer endpoints studied in relation to pesticide use, only one epidemiology study is available (De Roos *et al*., 2005); however, for NHL and other non-solid tumors, several investigations are published.

A. Cohort Studies

The eight cohort studies are discussed separately; however, they are really individual analyses and publications from the same cohort of the AHS prospective assessment (Alavanja *et al.,* 2003; Flower *et al*., 2004; De Roos *et al*., 2005; Engel *et al*., 2005; Lee *et al*., 2007; Landgren et al., 2009; Andreotti *et al*., 2009; and Dennis *et al*., 2010). It should be noted that there is some overlap between the cases and person-time reported findings in the AHS.

B. Case-Control Studies

Three case-control studies conducted by the National Cancer Institute in Iowa and Minnesota during the 1980s were reported by Brown *et al.* (1990), Cantor *et al.* (1992) and Brown *et al.* (1993).

De Roos *et al*. (2003) and Lee *et al*. (2004a) reported the results of case-control studies conducted in Iowa, Minnesota, Nebraska and/or Kansas in the U.S.A.

The Canadian population based case-control studies were reported by (McDuffie *et al*., 2001; Hohenadel *et al*., 2011; Karunanayke *et al*., 2012; and Kachuri *et al*., 2013).

Results of the Swedish case-control studies were reported by Nordstrom *et al*., 1998; Hardell and Erikson, 1999 and Hardell *et al*., 2002; and Eriksson *et al*., 2008).

A single case-control study conducted in France was reported by Orsi *et al.* (2009).

Coco *et al.*, (2013) reported the results of a pooled analyses of case-control studies conducted in six European countries between 1998 and 2004.

Case-control studies on the cancer of the brain (mainly gliomas) were reported by Ruder *et al.* 2004; Carreon *et al.*, 2005; Lee *et al.*, 2005; and Yiin *et al.*, 2012.

Case-control studies on other cancer sites were reported by Alavanja *et al.*, 2004 (lung); Bank *et al.*, 2011 and Koutros *et al.*, 2013 (prostate); Pahwa *et al.*, 2012 (soft tissue sarcoma) and Lee *et al.*, 2004b (stomach and esophagus).

Schinasi and Leon (2014) conducted a meta-analyses of the six studies that evaluated NHL and glyphosate exposure (McDuffie *et al.*, 2001; Hardell *et al.*, 2002; DeRoos *et al.*, 2003; 2005; Eriksson *et al.*, 2008; and Orsi *et al.*, 2009). Sorahan (2015) conducted a re-analyses of the multiple myeloma in the U.S Agricultural Health Study.

C. Results

A summary of the studies evaluating the association between glyphosate and cancer are discussed below.

- Results of the studies reporting data on solid tumors (non- lympho-hematopoietic) at various anatomical sites are presented in Table 2.

- Results of the studies reporting data on glyphosate and non-solid tumors (lymphohematopoietic) are presented in Table 3.

1. Solid Tumor Cancer Studies

Within the AHS study cohort, a number of authors evaluated several anatomical cancer sites in relation to pesticide use. A discussion of studies outside of the AHS cohort that addressed pesticide use in relation to non-solid tumors including multiple myeloma and NHL is presented below in Section C. 2 (Non-Solid Tumor Sites).

(i) Cancer at Multiple Sites

De Roos *et al.*, (2005) evaluated associations between glyphosate exposure and cancer incidence in the AHS cohort study of 57,311 licensed pesticide applicators in Iowa and North Carolina. The authors used poisson regression to estimate exposure-response relationship between glyphosate and incidence of all cancers combined and 12 relatively common cancer subtype. Exposure to glyphosate was not associated with all cancers combined [Odds Ratio (OR) =1.0 with 95% Confidence Interval (CI) of 0.90 - 1.2)] or specific anatomical cancer sites.

Several AHS nested case-control analyses also provide information concerning the carcinogenic potential of glyphosate. As presented in Table 2, there is no statistical evidence of an association with glyphosate presented across these studies. Specifically, AHS researchers reported no statistical evidence of an association between glyphosate use and cancers of the oral cavity (De Roos *et al.*, 2005), colon (De Roos *et al.*, 2005; Lee *et al.*, 2007), rectum (De Roos *et al.*, 2005; Lee *et al.*, 2007), lung (De Roos *et al.*, 2005), kidney (De Roos *et al.*, 2005), bladder (De Roos *et al.*, 2005), pancreas (De Roos *et al.*, 2005; Andreotti *et al.*, 2009), breast (Engel *et al.*, 2005), prostate (Alavanja *et al.*, 2003; Koutros *et al.*, 2013) or melanoma (De Roos *et al.*, 2005; Dennis *et al.*, 2010). The odds ratios (OR) and 95% confidence indices for these studies are provided in Table 2.

In a population-based study (Band *et al*, 2011) outside of the AHS, Canadian researchers reported non-significantly elevated odds of prostate cancer in relation to glyphosate use (OR=1.36; 95% CI= 0.83- 2.25). This study included prostate cancer cases between 1983-1990, prior to the prostate-specific antigen (PSA) era. Consequently, the study included more advanced tumors before diagnosis. Additionally, these data are in conflict with the results of Alavanja *et al.* (2003), which reflects the PSA-era cases (i.e., cases which are typically identified at an earlier stage in the progression of the disease). Koutros *et al.* (2013) did not identify an association with advanced prostate cancer (OR=0.93; 95% CI=0.73 - 1.18) in a prostate cancer follow-up study within the AHS.

A Canadian case-control study (Pahwa *et al.* 2011) examined exposure to pesticides and soft tissue sarcoma and found no relation with the use of glyphosate (OR=0.90; 95% CI= 0.58-1.40)].

Flower *et al.* (2004) examined the relation between parental pesticide use and all pediatric cancers reported to state registries among children of AHS participants and did not observe a significant association with maternal use exposure to glyphosate: (OR=0.61; 95% CI= 0.32 - 1.16) or paternal (prenatal) exposure to glyphosate: (OR=0.84; 95% CI= 0.35 - 2.54)

(ii) Brain (Glioma) Cancer

Lee *et al.* (2005) investigated the association between brain cancer with farming and agricultural pesticide use. The authors conducted telephone interviews of men and women diagnosed with gliomas (n = 251) between 1988 and 1993 in Nebraska and in controls (n = 498) identified from the same regions. Matching for age and vital-status, study authors reported a non-significant elevated odds of glioma (OR=1.5; 95% CI= 0.7 - 3.1) in relation to glyphosate use; however the results were significantly different between those who self-reported pesticide use (OR=0.4; 95% CI= 0.1- 1.6), and for those for whom a proxy respondent was used (OR=3.1; 95% CI=1.2 - 8.2), indicating recall bias was likely a characteristic of this study.

Three population-based case control studies evaluated the risk of brain cancer, specifically, glioma risk, among men and women participating in the Upper Midwest Health Study (*et al.*, 2005; Ruder *et al.*, 2004; Yiin *et al.*, 2012). Among glioma cases identified 1995-1997 Carreon, the authors found little evidence of a role for glyphosate in the etiology of this tumor. Herbicide use, including glyphosate was not-statistically significantly linked to glioma in either men (OR=1.51; 95% CI= 0.92 - 2.48) or women (0R 0.7; 95%CI=0.4-1.3). In a study by Carreon *et al.* (2005), there was no difference in risk estimate by vital status (use of self-report or proxy respondent), suggesting recall bias was more limited in this study in contrast to Lee *et al.* (2005). Using a quantitative measure of pesticide exposure (in contrast to an ever-use metric), the authors similarly observed no statistical evidence of an association with glyphosate; risk estimates were roughly equal to the null value (home and garden use: OR=0.98; 95% CI= 0.67 - 1.43); non-farm jobs: OR=0.83; 95% CI= 0.39 - 1.73) (Yiin *et al.*, 2012).

(iii) Stomach and Esophageal Cancers

In a population-based case control study in eastern Nebraska, Lee *et al.*, 2004) investigated pesticide use and stomach and esophageal adenocarcinomas. Cancer cases (stomach=170 and esophagus=137) were identified through the state cancer registry, and confirmed by a pathologist. The exposure assessment was based on self-reported pesticide use, with follow-up telephone interview to verify the reported information. There was no association between glyphosate exposure and either stomach cancer (OR=0.8; 95% CI= 0.4 - 1.5) or esophageal cancer (OR=0.7; 95% CI= 0.3 - 1.4).

Table 2. Summary of Findings: Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate Odds Ratio (OR) (95% Confidence Index (CI)**	**Conclusions**	**Potential Confounders Considered**
Cancer at Multiple Sites					
De Roos *et al*. (2005) AHS: Iowa and North Carolina, U.S.A	Cohort 1993-2001 54,315 licensed pesticide applicators	Self-report questionnaire; validated, reliability tested; adjusted for other pesticides	All cancers OR = 1.0; (0.9 -1.2)	No association between glyphosate exposure and all cancer including NHL.	Age at enrollment (continuous), education, cigarette smoking, alcohol consumption, family history of cancer in first degree relatives, and state of residence (dichotomous: Iowa/NC)
Site-Specific Cancers: Lung; Oral cavity; Colon; Rectum; Kidney; Bladder; Prostate and Melanoma					
De Roos *et al*. (2005) AHS: Iowa and North Carolina, U.S.A	Cohort 1993-2001 54,315 licensed pesticide applicators	Self-report questionnaire; validated, reliability tested; adjusted for other pesticides	Lung OR= 0.9; (0.6-1.3) Oral Cavity OR=1.0; (0.5-1.8) Colon OR=1.4; (0.8-2.2) Rectum OR=1.3; (0.7-2.3 Pancreas OR=0.7; (0.3-2.0) Kidney OR=1.6; (0.7-3.8) Bladder OR= 1.5; (0.7-3.2) Prostate OR=1.1; (09.-1.3) Melanoma OR=1.6; (0.8-3.0)	No significant association between glyphosate exposure and cancer of the lung, oral cavity, colon, rectum, pancreas, kidney, bladder, prostate or melanomas.	Age at enrollment (continuous), education, cigarette smoking, alcohol consumption, family history of cancer in first degree relatives, and state of residence (dichotomous: Iowa/NC)

Site-Specific Cancers: Breast Cancer					
Engel *et al.* (2005) AHS: Iowa and North Carolina, U.S.A	Nested Case-Control 1993-1997 30,454 wives of licensed pesticide applicators with no history of breast cancer at enrollment	Self-report questionnaire	Direct exposure (wives who applied) OR=0.9; 0.7-1.1) (Exposed: 82 cases 10,016 contorls) Indirect exposure (wives whose husbands applied) OR=1.3; (0.8-1.9) (Exposed: 109 cases 9,304, controls)	No association between glyphosate exposure and breast cancer	Age, race and state of residence (Iowa and North Carolina). Limited to licensed applicators. Potential exposure to multiple pesticides
Site-Specific Cancers: Pancreatic Cancer					
Andreotti *et al.* (2009) AHS: Iowa and North Carolina, U.S.A	Nested Case Control 1993-1997; follow-up to 2004; 93 cases 82,503 controls	Self-report questionnaire; validated, reliability tested	Ever-use OR= 1.1; (0.6, 1.7) (55 exposed cases)	No association between glyphosate exposure and pancreatic cancer	Age, smoke, diabetes, applicator type. Limited to licensed applicators. Potential exposure to multiple pesticides
Site-Specific Cancers: Prostate Cancer					
Alavanja *et al.* (2003) AHS: Iowa and North Carolina, U.S.A	Cohort 1993-1997; cancer thru 1999; 55,332 male applicators	Self-report questionnaire; validated, reliability tested	No quantitative risk estimate reported	No quantitative estimate due to lack of significant exposure-response association with prostate cancer.	Age, family history. Limited to licensed applicators. Potential exposure to multiple pesticides

Band *et al.* (2011) British Columbia, Canada	Case-Control 1983- 1990 1,516 prostate cancer patients 4,994 age-matched controls	Job exposure matrix for agriculture; detailed occupational history; exposure aggregated over all jobs reported. 60 exposed cases	OR=1.36; (0.83-2.25) (Exposed: 25 cases 60 controls)	No association between glyphosate exposure and prostate cancer	Alcohol consumption, cigarette years, education level, pipe smoking years and respondent
Koutros *et al.* (2013) AHS: Iowa and North Carolina, U.S.A	Nested Case Control 1993-2003 1,962 incident cases, including 919 aggressive prostate cancers among 54,412 applicators	Self-report questionnaire, validated	OR=0.93; (0.73-1.18)	No association between glyphosate exposure and prostate cancer	Age, state, race, family history of prostate cancer, smoking, fruit servings, and leisure-time physical activity in the winter

Site-Specific Cancers: Colorectal Cancer					
Lee *et al*. (2007) AHS: Iowa and North Carolina, U.S.A	Nested Case-Control 1993-97; follow-up to 2002 56,813 licensed pesticide applicators	Self-report questionnaire	Colon OR=1.0;(0.7-1.5) (Exposed: 151 cases 49 controls) Rectum OR=1.6; (0.9-2.9) (Exposed: 74 cases 18, controls) Colorectal (OR=1.2; (0.9-1.6) Exposed: 225 67 controls)	No significant association between glyphosate exposure and colon, rectum or colorectal cancer	Age, smoking, state, total days use pesticides. Limited to licensed applicators. Potential exposure to multiple pesticides
Site-Specific Cancers: Cutaneous Melanoma					
Dennis *et al.* (2010) AHS: Iowa and North Carolina, U.S.A	Nested Case-Control 1993-1997 150 cases, 24,554 non-cases	AHS self-report questionnaire	No quantitative risk estimate reported	No quantitative estimate due to lack of an association with cutaneous melanoma	Age, sex, tendency to burn, red hair, sun exposure time, BMI at 20 years
Site-Specific Cancers: Soft Tissue Sarcoma					
Pahwa *et al*., (2011) Canada	Case-Control 1991-1994 342 cases, 1506 age/resident matched controls	Self-reported use, structured interview/ questionnaire; cumulative exposure (+/-10 days/yr),	OR=0.90; (0.58-1.40)	No association between glyphosate exposure and soft tissue sarcoma	Significant medical history variables and with strata for the variables of age group and province of residence

Total Childhood Cancer					
Flower *et al*. (2004) AHS: Iowa and North Carolina, U.S.A	Cohort; hybrid prospective/ retrospective 1993-1998 21, 375 children of licensed pesticide applicators In Iowa (n=17,357) North Carolina (n=4018)	Self-report questionnaire; duration and frequency of pesticide use; Female Family questionnaire (child name)	Maternal use OR =0.61; (0.32, 1.16) 32 cases Paternal use (prenatal) OR=0.84; (0.35, 2.34);	No association was detected between frequency of parental pesticide application of glyphosate and childhood cancer risk.	Potential exposure to other pesticides. Child age in multiple logistic; [standardized incidence ratio (SIR)] was unadjusted
Brain Cancer (Glioma)					
Ruder *et al*. (2004) Upper Midwest Health Study (Iowa, Michigan, Minnesota and Wisconsin, U.S.A)	Population-based Case Control 1995-1997 457 glioma cases 648 population controls	Self-report questionnaire, with telephone based follow-up	No quantitative risk estimate reported for glyphosate.	No association with glyphosate exposure and brain cancer	Farm residence, age, use of other pesticides
Carreon et al. (2005) Upper Midwest Health Study (Iowa, Michigan, Minnesota and Wisconsin)	Population-based Case Control 1995-1997 341 glioma cases, 528 controls	Self-report questionnaire	Proxy respondents OR=0.75; (0.4-1.3) Exposed: 18 cases 41 Controls Excluding proxy OR=0.6; (0.3-1.2) Exposed:10 cases	No association with glyphosate exposure and brain cancer	Age, education and use of other pesticide

Lee et al. (2005a) Nebraska	Population based Case Control study 1988-1993; 251 glioma cases 498 controls	Self-reported questionnaire information, telephone follow-up for unclear responses; men and women assessed separately	Self-Report OR=0.4; (0.1- 1.6) Exposed: 4 cases 17 controls Overall OR=1.5; (0.7-3.1) Exposed: 17 cases 32 controls Proxy report OR:=3.1; (1.2- 8.2) Exposed:13 cases 15 controls	Non-significant excess risk for the overall group, but inconsistent for self-report and proxy indicating recall bias	Age, proxy, respond type
Esophagus and Stomach Cancer					
Lee et al. (2004b) Nebraska, U.S.A	Population based Case Control 1988-1993 137 esophageal cases; 170 stomach cases; 502 controls	Self-report pesticide use, telephone structured interview	Esophagus OR=0.7; (0.3-1.4) Exposed:12 cases 46 controls Stomach OR=0.8; (0.4-1.5) Exposed: 12 cases 46 controls	No association with glyphosate exposure and esophagus or stomach cancer	Age, sex

2. Non-Solid Tumor Sites (Lymph hematopoietic Cancers)

A number of studies evaluating the possible link between pesticide use and lymphohematopoietic cancers such as leukemia, multiple myeloma and NHL are presented in Table 3.

(i) Leukemia

In a population-based case control study in Iowa and Minnesota, Brown *et al.* (1990) investigated leukemia risk and pesticide use; authors did not observe an association with the ever-use of glyphosate in this study (OR= 0.9; 95% CI = 0.5 -1.6). The study population (578 cases; 340 living and 238 deceased and 1245 controls) was identified from cancers reported to state registry or authorities in 1981-1984, and the pesticide exposure assessment was performed through in-person interviews which the authors state likely reduced the exposure misclassification (incorrect exposure information). Although the large sample size is a strength of this study, the limitations include not controlling for exposure to other pesticides, limited power for studying the effects of glyphosate use, and the potential for recall bias.

In a Swedish population-based case control study, 121 cases in men and 484 controls matched for age and sex were identified in 1987-1992 through the Swedish cancer registry.The authors reported a non-statistically significant elevated risk of hairy cell leukemia in relation to glyphosate use (OR=3.1; 95% CI= 0.8 -12.0), controlling for age, sex, and residential location. However, because these results are based on only 4 glyphosate-exposed cases and 5 exposed controls as noted by the authors, this risk should be interpreted with caution. Also, there was limited power to detect an effect and there was no adjustment for other exposures. At this time, there is limited available literature concerning glyphosate use and leukemia (Nordstrom *et al.*, 1998).

(ii) Multiple Myeloma

In a follow-up analyses using the same study population from Iowa and Minnesota Brown *et al.* (1993) investigated whether pesticide use is also related to multiple myeloma. Among men in Iowa (173 cases, 605 controls), the authors observed a statistically non-significant elevated association with glyphosate use (OR=1.7; 95% CI = 0.80 - 3.6). However, the authors caution that while the study may lend support to the role of pesticides in general, the study limitations preclude use of the evidence as a definitive finding for any one compound.

De Roos *et al.* (2005) reported a suggestive association between multiple myeloma and glyphosate-exposed pesticide applicators based on a small number (32) of cases. For applicators with the full data set (54,315) and without adjustment for other variables the OR was 1.1; 95% CI, 0.5 – 2.4. In the fully adjusted model, there was a non-statistically significantly elevated risk (OR= 2.6; 95% CI= 0.70 - 9.4), however, the number of participants included in this analysis was lower (n=40,716) due to missing data for the covariates. The authors postulated that the increased

myeloma risk could be due to bias resulting from a selection of subjects in adjusted analyses that differed from subjects included in unadjusted analyses.

Lash *et al* (2007) performed a bias analysis of the De Roos *et al* (2005) data and reported that the frequency distribution generated by the bias analysis yielded a median hazard ratio equal to 1.5 with 95% simulation interval of 0.4 to 8.9, which was 66% wider than the conventional interval.

Sorahan (2015) using Poisson regression, re-analyzed the AHS data reported by De Roos *et al.* 2005) to examine the reason for the disparate findings in relation to the use of a full data set versus the restricted data set. Risk ratios were calculated for exposed and non-exposed subjects. When adjusted for age and sex, the OR was 1.12 with the 95% CI of 0.5 – 2.49 for ever-use of glyphosate. Additional adjustment for lifestyle factors and use of other pesticides did not have any effect (OR=1.24; 95% CI; 0.52 – 2.94).

In a population-based case control study among men in six Canadian provinces between 1991 and 1994, researchers reported non-statistically significantly elevated odds of multiple myeloma in relation to glyphosate use (OR=1.22; 95% CI= 0.77 - 1.93), based upon 32 glyphosate exposed multiple myeloma case and 133 controls [ADDIN EN.CITE <EndNote><Cite><Author>Pahwa</Author><Year>2012</Year><IDText>Multiple myeloma and exposure to pesticides: a Canadian case-control study</IDText><DisplayText>(Pahwa et al., 2012)</DisplayText><record><dates><pub-dates><date>Jan</date></pub-dates><year>2012</year></dates><keywords></keywords><isbn>1059-924x</isbn><titles><title>Multiple myeloma and exposure to pesticides: a Canadian case-control study</title><secondary-title>J Agromedicine</secondary-title><alt-title>Journal of agromedicine</alt-title></titles><pages>40-50</pages><number>1</number><contributors><authors><author>Pahwa, P.</author><author>Karunanayake, C. P.</author><author>Dosman, J. A.</author><author>Spinelli, J. J.</author><author>McDuffie, H. H.</author><author>McLaughlin, J. R.</author></authors></contributors><edition>2011/12/24</edition><language>eng</language><added-date format="utc">1374006867</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Canadian Centre for Health and Safety in Agriculture, University of Saskatchewan, Royal University Hospital, 103 Hospital Drive, Saskatoon, SK S7N 0W8, Canada. pup165@mail.usask.ca</auth-address><remote-database-provider>Nlm</remote-database-provider><rec-number>5519</rec-number><last-updated-date format="utc">1374006867</last-updated-date><accession-num>22191502</accession-num><electronic-resource-num>10.1080/1059924x.2012.632339</electronic-resource-num><volume>17</volume></record></Cite></EndNote>].

Kachuri *et al*. (2013), using the same Canadian study population as above, further explored multiple myeloma in relation to days per year glyphosate used in 342 cases of multiple myeloma and 1357 controls. For ever use, the OR=1.19; 95% CI=0.76-1.87. For light users (≤2 days/ year) there was no association (OR= 0.72; 95% CI= 0.39 -1.32; 15 exposed cases); whereas, for heavy

users (>2 days/ year), there was a non-significant increased odds ratio (OR= 2.04; 95% CI=0.98-4.23; 12 exposed cases). The limitation in this study was the same as the previous study (i.e, the number of cases and controls exposed to glyphosate were very low).

Within the AHS study population, [ADDIN EN.CITE <EndNote><Cite><Author>Landgren</Author><Year>2009</Year><IDText>Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study</IDText><DisplayText>(Landgren et al., 2009)</DisplayText><record><dates><pub-dates><date>Jun</date></pub-dates><year>2009</year></dates><urls><related-urls><url><Go to ISI>://000267147400021</url></related-urls></urls><titles><title>Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study</title><secondary-title>Blood</secondary-title></titles><pages>6386-6391</pages><number>25</number><contributors><authors><author>Landgren, O.</author><author>Kyle, R. A.</author><author>Hoppin, J. A.</author><author>Freeman, L. E. B.</author><author>Cerhan, J. R.</author><author>Katzmann, J. A.</author><author>Rajkumar, S. V.</author><author>Alavanja, M. C.</author></authors></contributors><added-date format="utc">1269462944</added-date><ref-type name="Journal Article">17</ref-type><rec-number>20</rec-number><last-updated-date format="utc">1384972707</last-updated-date><accession-num>ISI:000267147400021</accession-num><electronic-resource-num>10.1182/blood-2009-02-203471</electronic-resource-num><volume>113</volume></record></Cite></EndNote>], investigated the association between pesticide use and prevalence of monoclonal gammopathy of undetermined significance (or MGUS). The MGUS is considered a pre-clinical marker of multiple myeloma progression. The authors did not observe a link with glyphosate use in the AHS cohort (OR= 0.50; 95% CI = 0.20 -1.0).

(iii) Lymphoma

The National Cancer Institute (NCI) performed a series of population-based case control studies in the Midwestern U.S. in the early to mid-1980s. These studies include several hundred non-Hodgkin lymphoma (NHL) cases and controls, the identified cases were through disease registries which in many cases, were histopathologically confirmed. The investigators ascertained pesticide exposure through use of a structured interview with follow-up concerning pesticide use over time.

Cantor *et al* (1992), in a case-control study of NHL interviewed a total of 622 white men and 1245 population based-controls in Iowa and Minnesota. Only 26 cases and 49 controls ever handled glyphosate yielding an OR of 1.1 with the 95% CI of 0.7–1.9. The study, however, did not adjust for exposure to other pesticides.

[ADDIN EN.CITE <EndNote><Cite><Author>De Roos</Author><Year>2003</Year><IDText>Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men</IDText><DisplayText>(De Roos et al., 2003)</DisplayText><record><dates><pub-dates><date>Sep</date></pub-dates><year>2003</year></dates><urls><related-urls><url><Go to ISI>://000184904000029</url></related-urls></urls><titles><title>Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men</title><secondary-title>Occupational and Environmental Medicine</secondary-title></titles><number>9</number><contributors><authors><author>De Roos, A. J.</author><author>Zahm, S. H.</author><author>Cantor, K. P.</author><author>Weisenburger, D. D.</author><author>Holmes, F. F.</author><author>Burmeister, L. F.</author><author>Blair, A.</author></authors></contributors><added-date format="utc">1269462945</added-date><ref-type name="Journal Article">17</ref-type><rec-number>145</rec-number><last-updated-date format="utc">1269462945</last-updated-date><accession-num>ISI:000184904000029</accession-num><electronic-resource-num>e11</electronic-resource-num><volume>60</volume></record></Cite></EndNote>] used pooled analysis (n=3,417) of three case-control studies of NHL conducted in white men in Nebraska, Kansas and in Iowa and Minnesota. Based on 36 exposed cases and 61 exposed controls, the risk estimates for the association between glyphosate exposure and NHL was significant (OR=2.1; 95% CI=1.1- 4.0) in the logistic regression analyses. However, utilizing hierarchical regression techniques to adjust for exposure to other pesticide exposures, there was an increase risk, but the increase was not statistically significant (OR= 1.6; 95% CI = 0.90 - 2.8). Overall, the data showed a suggestive association.

Based on the above findings, Lee *et al*., (2004) examined the relationship between asthma and pesticide exposure, and NHL. Pooling data from several Midwestern (IA, MN, NE) states increased the study sample size, and additional pesticide use information was incorporated to adjust the risk estimate (duration and frequency of use, telephone follow-up interview). The study included 872 men with NHL and 2381 frequency-matched controls. The authors reported that the OR associated with glyphosate was not statistically significantly different among those with asthma (OR=1.2; 95%CI=0.4 -3.3; 6 exposed cases) and among those without asthma (OR=1.4; 95% CI =0.98 - 2.1; 53 exposed cases), adjusting for age, state and vital status.

The three studies discussed above (Cantor *et al*., 1992; De Roos *et al*., 2003 and Lee *et al*., 2004) reflect the same population in the AHS and used different levels of information (duration and frequency of exposure) and different analytic techniques [hierarchical regression and stratified analysis (by atopy)]. While studies with increasing levels of refinement to methodology report a

stronger risk estimates in relation to glyphosate, additional studies are needed to exclude the role of chance and other limitations that may explain positive (non-statistically significant) associations.

A population-based case–control study (Hardell and Erickson, 1999) investigated the exposure to pesticides as a risk factor for NHL in Sweden during 1987-1990. Exposure data were ascertained by comprehensive questionnaires and supplemented by telephone interviews. Of the 404 cases and 741 controls, only 4 glyphosate exposed cases and 3 controls were included in the study. In a univariate analysis, the risk estimate was elevated, but precision was low (OR= 2.3; 95% CI= 0.40 -13.0).

[ADDIN EN.CITE
<EndNote><Cite><Author>Hardell</Author><Year>2002</Year><IDText>Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies</IDText><DisplayText>(L. Hardell et al., 2002)</DisplayText><record><dates><pub-dates><date>May</date></pub-dates><year>2002</year></dates><keywords></keywords><isbn>1042-8194 (Print)
1026-8022</isbn><titles><title>Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies</title><secondary-title>Leuk Lymphoma</secondary-title><alt-title>Leukemia & lymphoma</alt-title></titles><pages>1043-9</pages><number>5</number><contributors><authors><author>Hardell, L.</author><author>Eriksson, M.</author><author>Nordstrom, M.</author></authors></contributors><edition>2002/08/01</edition><language>eng</language><added-date format="utc">1384293793</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Department of Oncology, Orebro University Hospital, Sweden. lennart.hardell@orebroll.se</auth-address><remote-database-provider>NLM</remote-database-provider><rec-number>5652</rec-number><last-updated-date format="utc">1384349385</last-updated-date><accession-num>12148884</accession-num><volume>43</volume></record></Cite></EndNote>] analyzed pooled data from two case-control studies from Sweden that examined NHL (Hardell and Erickson, 1999) and another on hairy cell leukemia, a subtype of NHL (Nordstrom *et al.*, 1998). In the univariate analysis glyphosate exposure was found to be significantly increased (OR=3.04; 95% CI=1.08 - 8.52) but, when study site, and vital status were considered in a multivariate analyses, there was a non-statistically elevated risk among glyphosate users (OR = 1.85; 95% CI= 0.55 - 6.20). However, the wide range of the CI suggest that the study is under powered and, therefore the findings do not allow definitive conclusion on the association of NHL and glyphosate exposure.

In another case-control study in Sweden (1999-2003), [ADDIN EN.CITE
<EndNote><Cite><Author>Eriksson</Author><Year>2008</Year><IDText>Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis</IDText><DisplayText>(Eriksson et al., 2008)</DisplayText><record><dates><pub-dates><date>Oct</date></pub-dates><year>2008</year></dates><urls><related-

urls><url><Go to ISI>://000258892500023</url></related-urls></urls><titles><title>Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis</title><secondary-title>International Journal of Cancer</secondary-title></titles><pages>1657-1663</pages><number>7</number><contributors><authors><author>Eriksson, M.</author><author>Hardell, L.</author><author>Carlberg, M.</author><author>Akerman, M.</author></authors></contributors><added-date format="utc">1269462944</added-date><ref-type name="Journal Article">17</ref-type><rec-number>32</rec-number><last-updated-date format="utc">1384789327</last-updated-date><accession-num>ISI:000258892500023</accession-num><electronic-resource-num>10.1002/ijc.23589</electronic-resource-num><volume>123</volume></record></Cite></EndNote>] examined the effects of exposure to different agents and NHL among 910 NHL cases and 1016 non-NHL controls. Glyphosate exposure which was reported in 29 cases and 18 controls produced an OR of 2.02 (95% CI of 1.10–3.71) in a univariate analysis and an OR of 1.51(95% CI of 0.77–2.94) in a multivariate analysis conducted to clarify the relative importance of exposure to different pesticides. When exposure was for more than 10 days/year, the OR was 2.36 (95% CI=1.16-4.40) and for exposure less than 10 days/year, the OR was 1.69 (95% CI=0.7-4.07). The risk estimate was elevated also for B-cell lymphoma and glyphosate exposure (OR=1.87; 95% CI=0.998-3.51).

McDuffie *et al* (2001) in a multicenter-population based study among men of six Canadian provinces estimated the association between glyphosate and NHL. The study included 517 cases and 1506 controls identified betwen1991and 1994 through provincial cancer registries. In this study, authors histopathologically confirmed 84% of cases implemented a two-tiered exposure questionnaire; and assessed the validity of the questionnaire through quality control studies both of which increased the accuracy of the test results. There was a non-statistically significant increased risk of NHL from glyphosate exposure. The OR was 1.26 and the 95% CI was 0.87–1.80 for 51 exposed cases, adjusted for age and province and the OR was 1.20 with a 95% CI of 0.83–1.74 when adjusted for age, province and high-risk exposure (adjusted for statistically significant medical variables such as history of measles, mumps, cancer, allergy desensitization shots, and a positive family history of cancer in a first-degree relative).

In a follow-up study which controlled for exposure to other pesticides, the risk to NHL from glyphosate exposure was attenuated. Glyphosate exposure which was reported in 19 cases and 78 controls produced an OR of 0.92 with 95% CI of 0.5–1.55 [ADDIN EN.CITE <EndNote><Cite><Author>Hohenadel</Author><Year>2011</Year><IDText>Exposure to multiple pesticides and risk of non-Hodgkin lymphoma in men from six Canadian provinces</IDText><DisplayText>(Hohenadel et al., 2011)</DisplayText><record><dates><pub-dates><date>Jun</date></pub-dates><year>2011</year></dates><keywords></keywords><isbn>1660-4601</isbn><custom2>Pmc3138027</custom2><titles><title>Exposure to multiple pesticides and risk of non-Hodgkin lymphoma in men from six Canadian provinces</title><secondary-title>Int J Environ Res Public Health</secondary-title><alt-title>International journal of environmental

research and public health</alt-title></titles><pages>2320-30</pages><number>6</number><contributors><authors><author>Hohenadel, K.</author><author>Harris, S. A.</author><author>McLaughlin, J. R.</author><author>Spinelli, J. J.</author><author>Pahwa, P.</author><author>Dosman, J. A.</author><author>Demers, P. A.</author><author>Blair, A.</author></authors></contributors><edition>2011/07/22</edition><language>eng</language><added-date format="utc">1373466563</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Occupational Cancer Research Centre, 505 University Avenue, 14th floor, Toronto, Ontario M5G 1X3, Canada. karin.hohenadel@cancercare.on.ca</auth-address><remote-database-provider>Nlm</remote-database-provider><rec-number>4600</rec-number><last-updated-date format="utc">1373467057</last-updated-date><accession-num>21776232</accession-num><electronic-resource-num>10.3390/ijerph8062320</electronic-resource-num><volume>8</volume></record></Cite></EndNote>]. Within this series of studies, the authors also evaluated Hodgkin's lymphoma (HL), and similarly observed little statistical evidence of an association, using similar study design and methods. Among the 38 cases exposed to glyphosate the OR was 0.99 with the 95% CI of 0.62 - 1.56 [ADDIN EN.CITE <EndNote><Cite><Author>Karunanayake</Author><Year>2012</Year><IDText>Hodgkin lymphoma and pesticides exposure in men: a Canadian case-control study</IDText><DisplayText>(Karunanayake et al., 2012)</DisplayText><record><dates><pub-dates><date>Jan</date></pub-dates><year>2012</year></dates><keywords></keywords><urls><related-urls><url>http://www.ncbi.nlm.nih.gov/pubmed/22191501</url></related-urls></urls><isbn>1545-0813</isbn><titles><title>Hodgkin lymphoma and pesticides exposure in men: a Canadian case-control study</title><secondary-title>J Agromedicine</secondary-title></titles><pages>30-9</pages><number>1</number><contributors><authors><author>Karunanayake, C. P.</author><author>Spinelli, J. J.</author><author>McLaughlin, J. R.</author><author>Dosman, J. A.</author><author>Pahwa, P.</author><author>McDuffie, H. H.</author></authors></contributors><language>eng</language><added-date format="utc">1391104896</added-date><ref-type name="Journal Article">17</ref-type><rec-number>5694</rec-number><last-updated-date format="utc">1391104896</last-updated-date><accession-num>22191501</accession-num><electronic-resource-num>10.1080/1059924X.2012.632726</electronic-resource-num><volume>17</volume></record></Cite></EndNote>].

In a hospital-based case control study conducted between 2000 and 2004 in France, authors identified 491 NHL cases and 456 age-and sex-matched controls, and performed telephone-based questionnaire to assess pesticide and other confounding variables. There was no association between NHL and glyphosate use; for the 12 exposed cases, the OR was 1.0 and the 95% CI was 0.50 - 2.2) For Hodgkin's lymphoma, for the 6 exposed cases, the OR was 1.7 and the 95% CI was 0.6-5[ADDIN EN.CITE <EndNote><Cite><Author>Orsi</Author><Year>2009</Year><IDText>Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control

study</IDText><DisplayText>(Orsi et al., 2009)</DisplayText><record><dates><pub-dates><date>May</date></pub-dates><year>2009</year></dates><urls><related-urls><url><Go to ISI>://000265274700003</url></related-urls></urls><titles><title>Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study</title><secondary-title>Occupational and Environmental Medicine</secondary-title></titles><pages>291-298</pages><number>5</number><contributors><authors><author>Orsi, L.</author><author>Delabre, L.</author><author>Monnereau, A.</author><author>Delval, P.</author><author>Berthou, C.</author><author>Fenaux, P.</author><author>Marit, G.</author><author>Soubeyran, P.</author><author>Huguet, F.</author><author>Milpied, N.</author><author>Leporrier, M.</author><author>Hemon, D.</author><author>Troussard, X.</author><author>Clavel, J.</author></authors></contributors><added-date format="utc">1269462944</added-date><ref-type name="Journal Article">17</ref-type><rec-number>22</rec-number><last-updated-date format="utc">1384972839</last-updated-date><accession-num>ISI:000265274700003</accession-num><electronic-resource-num>10.1136/oem.2008.040972</electronic-resource-num><volume>66</volume></record></Cite></EndNote>].

The EPILYMPH case-control study was conducted across six countries in Europe (Czech Republic, France, Germany, Ireland, Italy, and Spain) to explore the role of occupational exposure to specific chemicals and lymphoma, B-cell lymphoma and subtypes. Although the study recruited 2348 cases and 2462 controls, only a very small number of cases were exposed to glyphosate (n=4) and controls (n=2). A non-significant increase in OR was observed for B-cell lymphoma (OR=3.1; 95% CI= 0.6-17.1), but the estimate is unstable due to the small number of exposed cases and controls (Cocco *et al.* 2013)

Schinasi and Leon (2014) conducted a meta-analysis exploring occupational glyphosate exposure and NHL utilizing six of the above mentioned studies (McDuffie *et al.* 2001; Hardell *et al.* 2002; DeRoos *et al.* 2003 and 2005; Eriksson *et al.* 2008; and Orsi *et al.* 2009). Since the authors identified a variety of sources of heterogeneity between publications, they calculated meta- risk ratio (RR) estimates and 95% CIs using random effect models, allowing between study heterogeneity to contribute to the variance. They reported I^2 values, which represented the percentage of the total variance explained by study heterogeneity and measure inconsistency in results. Larger I^2 values indicate greater inconsistency. For glyphosate, the meta risk-ratio was 1.5 with a 95% CI of 1.0-2.0 and the I^2 value was 32.7% indicating greater inconsistency in these data set. This study combined multiple smaller studies that on their own were very limited in statistical power to detect differences.

The 2015 IARC evaluation noted that two of the Swedish studies (Hardell *et a*l. 2002 and Eriksson *et al.* 2008) fully adjusted risk estimates were not used in the analysis conducted by Schinasi and Leon (2014). Consequently, IARC conducted a reexamination of the results of these studies. For an association between glyphosate exposure and NHL, the IARC estimated meta-risk ratio of 1.3 (95% CI was 1.03-1.65), I^2 = 0%, p=0.589, for heterogeneity was updated and calculated (IARC

2015).

Table 3. Summary of Findings: Non Solid Tumor Cancer Studies					
Study	**Study Design**	**Exposure Assessment**	**Risk Estimate Odds Ratio (OR) (95% CI)**	**Conclusions**	**Potential Confounders Considered**
Leukemia					
Brown *et al.* (1990) Iowa and Minnesota, U.S.A	Population based Case-Control 1981-1984 578 cases 1245 controls	In person interview; surrogates used.	OR=0.9; (0.5-1.6) Exposed:15 cases 49 controls	No association with glyphosate exposure and leukemia	Vital status (alive, dead), residency (IA or MN), tobacco use, parent, sibling, or child with a lymphopoietic cancer, high risk occupation and exposure to substances (benzene, hair dyes etc) related to risk of leukemia
Nordstrom *et al.* (1998) Sweden	Population based Case-Control 1987-1992 121 cases 484 controls	Self-reported pesticide questionnaire and follow-up telephone interview	OR=3.1 (0.8-12) Exposed: 4 cases 5 controls	A non-statistically significant elevated risk of hairy cell leukemia.	Age, sex, country of residence (selected using matching, dissolved matching analyses). No adjustment for exposure from other pesticides
Multiple Myeloma					
Brown *et al.* (1993) Iowa, U.S.A	Population based Case-Control 1981-1984 173cases 650 controls	Interview based questionnaire with follow-up	OR=1.7; (0.8-3.6) Exposed: 11 cases 40 controls	Limited power to assess association of glyphosate exposure and multiple myeloma	Age and vital status

De Roos *et al*. (2005) Iowa and North Carolina, U.S.A	Prospective Cohort 1993-2001 54,315 licensed pesticide applicators	Self-administered questionnaire	Full data set OR =1.1; (0.5 – 2.4) Exposed: 32 cases Adjusted for age etc OR=2.6; (0.7-9.4)	No risk for full data set. Excess risk only with no missing information of 22 cases in the restricted data set (Sorahan, (2015)	Missing data on covariates when multiple adjustments were made, limiting interpretation
[ADDIN EN.CITE <EndNote><Cite><Author>Orsi</Author><Year>2009</Year><IDText>Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study</IDText><DisplayText>(Orsi et al., 2009)</DisplayText><record><dates><pub-dates><date>May</date></pub-dates><year>2009</year></dates><urls><related-urls><url><Go to ISI>://0002652747	Hospital based Case-Control 2000-2004 491 cases 456 controls	Self-report questionnaire, with follow-up telephone based questionnaire, expert review; two stage exposure collection process	OR=2.4; (0.8-7.3) Exposed: 5 cases 18 controls	No significant association with glyphosate exposure and multiple myeloma	Age, center, socioeconomic category

00003</url></related-urls></urls><titles><title>Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study</title><secondary-title>Occupational and Environmental Medicine</secondary-title></titles><pages>291-298</pages><number>5</number><contributors><authors><author>Orsi, L.</author><author>Delabre, L.</author><author>Monnereau, A.</author><author>Delval, P.</author><author>Berthou, C.</author><author>Fenaux, P.</author><author>Marit, G.</author><author>Soubeyran, P.</author><author>H					

uguet, F.</author><author> Milpied, N.</author><author> Leporrier, M.</author><author> Hemon, D.</author><author> Troussard, X.</author><author> Clavel, J.</author></authors> </contributors><added -date format="utc">126946 2944</added- date><ref-type name="Journal Article">17</ref- type><rec- number>22</rec- number><last- updated-date format="utc">138497 2839</last-updated- date><accession- num>ISI:0002652747 00003</accession- num><electronic- resource- num>10.1136/oem.20 08.040972</electronic -resource-					

num><volume>66</volume></record></Cite></EndNote>]). France					
[ADDIN EN.CITE <EndNote><Cite><Author>Pahwa</Author><Year>2012</Year><IDText>Multiple myeloma and exposure to pesticides: a Canadian case-control study</IDText><DisplayText>(Pahwa et al., 2012)</DisplayText><record><dates><pub-dates><date>Jan</date></pub-dates><year>2012</year></dates><keywords></keywords><isbn>1059-924x</isbn><titles><title>Multiple myeloma and	Population based Case-Control 1991-1994 342 cases 1506 controls	Self-reported pesticide use, structured interview with questionnaire; cumulative exposure (+/-10 days/yr),	OR=1.22; (0.77 - 1.93) Exposed: 32 cases 133 controls	No significant association with glyphosate exposure and multiple myeloma	Significant medical history variables (history of measles, history of mumps, history of allergies, history of arthritis, history of shingles, and a positive family history of cancer in a first-degree relative), and with strata for the variables of age group and province of residence

exposure to pesticides: a Canadian case-control study</title><secondary-title>J Agromedicine</secondary-title><alt-title>Journal of agromedicine</alt-title></titles><pages>40-50</pages><number>1</number><contributors><authors><author>Pahwa, P.</author><author>Karunanayake, C. P.</author><author>Dosman, J. A.</author><author>Spinelli, J. J.</author><author>McDuffie, H. H.</author><author>McLaughlin, J. R.</author></authors></contributors><edition>2011/12/24</edition><language>eng</language><added-date format="utc">1374006867</added-date><ref-type					

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olume></record></Cite></EndNote>] Canada					
Kachuri *et al.* (2013) Canadian Provinces	Population based Case-Control 1991-1994 342 cases 1357 controls	Self-administered questionnaire	<u>For ever use</u> OR=1.19; (0.76-1.87) Exposed: 32 cases 121controls <u>Light (<2 d/yr) use</u> OR= 0.72; (0.39 -1.32) Exposed: 15 cases 88 controls <u>Heavy (>2 d/yr) use</u> OR=2.04; (0.98-4.23) Exposed: 12 cases 29 controls	No association with glyphosate exposure and multiple myeloma for ever or light users Increase for heavy users is non-significant	Relatively low response rate
Monoclonal Gammopathy of Undetermined Significance (MGUS)					
[ADDIN EN.CITE <EndNote><Cite><Author>Landgren</Author><Year>2009</Year><IDText>Pesticide exposure and risk of monoclonal	Prospective Cohort study 1993-1997 678 participants	Self-administered questionnaire	OR=0.5; (0.2-1.0)	No association with glyphosate exposure and MGUS, a premalignant disorder that often precedes multiple myeloma	Age and education

gammopathy of undetermined significance in the Agricultural Health Study</IDText><DisplayText>(Landgren et al., 2009)</DisplayText><record><dates><pub-dates><date>Jun</date></pub-dates><year>2009</year></dates><urls><related-urls><url><Go to ISI>://000267147400021</url></related-urls></urls><titles><title>Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study</title><secondary-title>Blood</secondary-title></titles><pages>6386-6391</pages><numbe					

r>25</number><contributors><authors><author>Landgren, O.</author><author>Kyle, R. A.</author><author>Hoppin, J. A.</author><author>Freeman, L. E. B.</author><author>Cerhan, J. R.</author><author>Katzmann, J. A.</author><author>Rajkumar, S. V.</author><author>Alavanja, M. C.</author></authors></contributors><added-date format="utc">1269462944</added-date><ref-type name="Journal Article">17</ref-type><rec-number>20</rec-number><last-updated-date format="utc">1384972707</last-updated-date><accession-num>ISI:0002671474					

00021</accession-num><electronic-resource-num>10.1182/blood-2009-02-203471</electronic-resource-num><volume>113</volume></record></Cite></EndNote>] AHS: Iowa and North Carolina, U.S.A					
Non Hodgkins Lymphoma (NHL)					
Cantor *et al.* (1992) Iowa and Minnesota, U.S.A	Population based Case-Control 1980-1983 622 cases 1245 controls	Structured interview, questionnaire response; farm activities and specific pesticide use	OR=1.1; (0.7-1.9) Exposed: 26 cases 49 controls	No association with glyphosate exposure and NHL	Vital status, age, state, smoking, family history, high risk occupation, high risk exposure. Not controlled for exposure to other pesticides.

De Roos *et al.* (2003) Iowa, Nebraska, Minnesota, Kansas, U.S.A	Case-Control 1979-1986 870 cases 2569 controls	Interview-based questionnaire, demographic	Logistic regression OR=2.1; (1.1-4.0) Exposed: 36 cases 61 controls Hierarchical regression OR=1.6; (0.9-2.8)	Statistically significant in the logistic regression analyses. Elevated but no statistically significant in hierarchical regression	Age, study site, use of all other pesticides (group); hierarchal regression informed priors based on chemical-specific information
Lee *et al*., (2004a) Iowa, Nebraska, Minnesota, U.S.A	Population based Case-Control 1980-1986 872 cases 2381controls	In person, structured interview (pesticide use, duration, frequency, first and last year used); 5-yr follow-up interview, 10-min telephone on pesticide use	Non-asthmatic OR=1.4; (0.98-2.1) Exposed: 53 cases 91 controls Asthmatic OR=1.2 (0.4-3.3) Exposed: 6 cases 12 controls	No significant association with glyphosate exposure and NHL either for asthmatics or non-asthmatics	A adjusted for age, vital status, state
De Roos *et al.* (2005) AHS: Iowa and North Carolina, U.S.A	Cohort 1993-2001 54,315 licensed pesticide applicators	Self-administered questionnaire	OR= 1.1; (0.7-1.9 Ex2posed: 9	No association of NHL with glyphosate exposure	Age, smoking, other pesticides, alcohol consumption, family history of cancer, education
Hardell and Erickson, (1999) Sweden	Population based Case-Control 1987-1990 404 cases 741 controls	Questionnaire and follow-up interview	Univariate OR=2.3; (0.4-13.0) Exposed: 4 cases 3 controls Multivariate OR=5.8; (0.6-54)	Some evidence of a link with glyphosate, matching variables; cannot conclude regarding causal role for any specific pesticide	Age, region, vital status (matching). Few subjects exposed. Variables used in multivariate were no specified. Study has limited power to detect an effect

[ADDIN EN.CITE <EndNote><Cite><Author>Hardell</Author><Year>2002</Year><IDText>Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies</IDText><DisplayText>(L. Hardell et al., 2002)</DisplayText><record><dates><pub-dates><date>May</date></pub-dates><year>2002</year></dates><keywords></keywords><isbn>1042-8194 (Print)
1026-8022</isbn><titles><title>Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two	Population based Case-Control 1987-1990 515 cases 1141 controls	Questionnaire and follow-up interview	Univariate OR=3.04; (1.08-8.52) Exposed: 8 cases 8 controls Multivariate OR=1.85; (0.55-6.20)	Risk attenuates when adjusted for other variables in the multivariate analysis	Age, country, study site, vital status, other pesticide exposure in the multivariate analysis. Overlaps with Hardell and Erickson, 1999 and Nordstrom et al., 1998.

Swedish case-control studies</title><secondary-title>Leuk Lymphoma</secondary-title><alt-title>Leukemia & lymphoma</alt-title></titles><pages>1043-9</pages><number>5</number><contributors><authors><author>Hardell, L.</author><author>Eriksson, M.</author><author>Nordstrom, M.</author></authors></contributors><edition>2002/08/01</edition><language>eng</language><added-date format="utc">1384293793</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Department of Oncology, Orebro University Hospital, Sweden. lennart.hardell@orebr					

oll.se</auth-address><remote-database-provider>NLM</remote-database-provider><rec-number>5652</rec-number><last-updated-date format="utc">1384349385</last-updated-date><accession-num>12148884</accession-num><volume>43</volume></record></Cite></EndNote>] Sweden					
[ADDIN EN.CITE <EndNote><Cite><Author>Eriksson</Author><Year>2008</Year><IDText>Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis</IDText><DisplayText>(Eriksson et al., 2008)</DisplayText>	Population based Case-Control 1999-2002 910 cases 1016 controls	Questionnaire and follow-up interview	Univariate OR= 2.02 (1.10-3.71) Exposed: 29 cases 18 controls Multivariate OR=1.55; (0.77-2.94) With <10 days/ year OR=1.69; (0.7-4.07) Exposed: 12 cases 9 controls With > 10 days/year	Suggestive association for NHL with glyphosate exposure.	Age, sex, year of diagnosis. Multivariate analysis adjusted for exposure to other pesticides

<record><dates><pub-dates><date>Oct</date></pub-dates><year>2008</year></dates><urls><related-urls><url><Go to ISI>://000258892500023</url></related-urls></urls><titles><title>Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis</title><secondary-title>International Journal of Cancer</secondary-title></titles><pages>1657-1663</pages><number>7</number><contributors><authors><author>Eriksson, M.</author><author>Hardell, L.</author><author>Carlberg, M.</author><author>			OR=2.36; (1.04-5.37) Exposed: 17 cases 9 controls B-cell lymphoma OR=1.87; (0.998-3.51)		

Akerman, M.</author></authors></contributors><added-date format="utc">1269462944</added-date><ref-type name="Journal Article">17</ref-type><rec-number>32</rec-number><last-updated-date format="utc">1384789327</last-updated-date><accession-num>ISI:000258892500023</accession-num><electronic-resource-num>10.1002/ijc.23589</electronic-resource-num><volume>123</volume></record></Cite></EndNote>] Sweden					

McDuffie *et al* (2001) Canada	Population based Case-Control 1991-1994 517 cases 1506 controls	Two-tiered self-report questionnaire; cumulative exposure (≥ 10 days/yr)	Univariate OR=1.26; (0.87-1.8) Exposed: 51 cases 133 controls Multivariate OR=1.20; (0.83-1.74)	No significant association with glyphosate exposure and NHL	Adjusted for statistically significantly medical variables (history of measles, mumps, cancer, allergy shots, and a positive family history of cancer) males only
[ADDIN EN.CITE <EndNote><Cite><Author>Hohenadel</Author><Year>2011</Year><IDText>Exposure to multiple pesticides and risk of non-Hodgkin lymphoma in men from six Canadian provinces</IDText><DisplayText>(Hohenadel et al., 2011)</DisplayText><record><dates><pub-dates><date>Jun</date></pub-dates><year>2011</year></dates><keywords></keywords><isbn	Case-Control 1991-1994 513 cases 1506 controls	Two-tiered self-report questionnaire; cumulative exposure (≥ 10 days/yr)	OR=0.92; (0.54-1.55) Exposed: 19 cases 78 controls	No significant association with glyphosate exposure and NHL	Age, province and proxy respondent, males only

>1660-4601</isbn><custom2>Pmc3138027</custom2><titles><title>Exposure to multiple pesticides and risk of non-Hodgkin lymphoma in men from six Canadian provinces</title><secondary-title>Int J Environ Res Public Health</secondary-title><alt-title>International journal of environmental research and public health</alt-title></titles><pages>2320-30</pages><number>6</number><contributors><authors><author>Hohenadel, K.</author><author>Harris, S. A.</author><author>McLaughlin, J. R.</author><author>Spinelli, J. J.</author><author>Pahwa,					

P.</author><author>Dosman, J. A.</author><author>Demers, P. A.</author><author>Blair, A.</author></authors></contributors><edition>2011/07/22</edition><language>eng</language><added-date format="utc">1373466563</added-date><ref-type name="Journal Article">17</ref-type><auth-address>Occupational Cancer Research Centre, 505 University Avenue, 14th floor, Toronto, Ontario M5G 1X3, Canada. karin.hohenadel@cancercare.on.ca</auth-address><remote-database-provider>Nlm</remote-database-provider><rec-number>4600</rec-number><last-updated-date					

format="utc">1373467057</last-updated-date><accession-num>21776232</accession-num><electronic-resource-num>10.3390/ijerph8062320</electronic-resource-num><volume>8</volume></record></Cite></EndNote>] Canada					
[ADDIN EN.CITE <EndNote><Cite><Author>Orsi</Author><Year>2009</Year><IDText>Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study</IDText><DisplayText>(Orsi et al., 2009)</DisplayText><record><dates><pub-dates><date>May</date></pub-dates><year>2009</y	Hospital based Case-Control 2000-2004 491 cases 456 controls	Self-report questionnaire, with follow-up telephone based questionnaire, expert review; two stage exposure collection process	NHL OR=1.0; (0.5-2.2) Exposed:12 cases 24 controls Multiple Myeloma OR=2.4; (0.8-7.3) Exposed 5 cases 18 controls	No association with glyphosate exposure and NHL	Age, center, socioeconomic category

ear></dates><urls><related-urls><url><Go to ISI>://000265274700003</url></related-urls></urls><titles><title>Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study</title><secondary-title>Occupational and Environmental Medicine</secondary-title></titles><pages>291-298</pages><number>5</number><contributors><authors><author>Orsi, L.</author><author>Delabre, L.</author><author>Monnereau, A.</author><author>Delval, P.</author><author>Berthou, C.</author><author>Fenaux, P.</author><author>					

Marit, G.</author><author>Soubeyran, P.</author><author>Huguet, F.</author><author> Milpied, N.</author><author> Leporrier, M.</author><author> Hemon, D.</author><author> Troussard, X.</author><author> Clavel, J.</author></authors> </contributors><added -date format="utc">1269462944</added-date><ref-type name="Journal Article">17</ref-type><rec-number>22</rec-number><last-updated-date format="utc">1384972839</last-updated-date><accession-num>ISI:000265274700003</accession-num><electronic-					

resource-num>10.1136/oem.2008.040972</electronic-resource-num><volume>66</volume></record></Cite></EndNote>]). France					
Cocco *et al.* (2013) Czech Republic, France, Germany, Italy, Ireland and Spain	EPICLYMPH Case-Control 1998–2003 2348 cases 2462 controls	Occupational exposure Trained interviewers conducted in person interviews with cases and controls	OR=3.1; (0.6-17.1) Exposed: 4 cases 2 controls	No significant association with glyphosate exposure and B-cell	Age, centre, socioeconomic category.
Hodgkin's Lymphoma					
[ADDIN EN.CITE <EndNote><Cite><Author>Orsi</Author><Year>2009</Year><IDText>Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study</IDText><DisplayText>(Orsi et al.,	Hospital based Case-Control 2000-2004 491 cases 456 controls	Self-report questionnaire, with follow-up telephone based questionnaire, expert review; two stage exposure collection process	<u>Hodgkin's lymphoma</u> OR=1.7; (0.6-5.0) Exposed: 6 cases 15 controls	No significant association with glyphosate exposure and HL	Age, center, socioeconomic category

2009)</DisplayText><record><dates><pub-dates><date>May</date></pub-dates><year>2009</year></dates><urls><related-urls><url><Go to ISI>://000265274700003</url></related-urls></urls><titles><title>Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study</title><secondary-title>Occupational and Environmental Medicine</secondary-title></titles><pages>291-298</pages><number>5</number><contributors><authors><author>Orsi, L.</author><author>Delabre, L.</author><author>Monnereau, A.</author><author>					

Delval, P.</author><author>Berthou, C.</author><author>Fenaux, P.</author><author> Marit, G.</author><author>Soubeyran, P.</author><author>Huguet, F.</author><author> Milpied, N.</author><author> Leporrier, M.</author><author> Hemon, D.</author><author> Troussard, X.</author><author> Clavel, J.</author></authors> </contributors><added -date format="utc">1269462944</added-date><ref-type name="Journal Article">17</ref-type><rec-number>22</rec-number><last-updated-date					